Amendments to the Specification:

Please replace the paragraph beginning at page 1, line 9 (immediately after the title) with the following rewritten paragraph:

> The present application is a ~~continuation~~ division of USSN 09/383,667, now ~~allowed~~ U.S. Pat. No. 6,624,295; which claims priority under 35 U.S.C. § 119 to provisional application numbers 60/122,767, filed March 3, 1999 and 60/098,233, filed August 28, 1998, both abandoned.

Please replace the paragraphs beginning on page 12, line 23 and ending on page 13, line 6 with the following amended paragraph:

The term "~~treatment~~" as used within the context of the present invention is meant to include therapeutic treatment as well as prophylactic, or suppressive measures for the disease or disorder. Thus, for example, the term treatment includes the administration of an agent prior to or following the onset of a disease or disorder thereby preventing or removing all signs of the disease or disorder. As another example, administration of the agent after clinical manifestation of the disease to combat the symptoms of the disease comprises "~~treatment~~" of the disease. Further, administration of the agent after onset and after clinical symptoms have developed where administration affects clinical parameters of the disease or disorder and perhaps amelioration of the disease, comprises "~~treatment~~" of the disease.

Those "~~in need of treatment~~" include mammals, such as humans, already having the disease or disorder, including those in which the disease or disorder is to be prevented.

Please replace the paragraph beginning on page 50, line25 and ending on page 51, line 19 with the following rewritten paragraph:

The antibodies of the invention may be prepared in a mixture with a pharmaceutically acceptable carrier. This therapeutic composition can be administered intravenously or through the nose or lung, preferably as a liquid or powder aerosol (lyophilized). The composition may

also be administered parenterally or subcutaneously as desired. When administered systematically, the therapeutic composition should be sterile, pyrogen-free and in a parenterally acceptable solution having due regard for pH, isotonicity, and stability. These conditions are known to those skilled in the art. Briefly, dosage formulations of the compounds of the present invention are prepared for storage or administration by mixing the compound having the desired degree of purity with physiologically acceptable carriers, excipients, or stabilizers. Such materials are non-toxic to the recipients at the dosages and concentrations employed, and include buffers such as TRIS HCl, phosphate, citrate, acetate and other organic acid salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) peptides such as polyarginine, proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidinone; amino acids such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium and/or nonionic surfactants such as TWEEN®, ~~PLURONICS~~Pluronics or polyethyleneglycol.

Please replace the paragraph on page 53, lines 1-18 with the following amended paragraph:

Reagents. FIX and FXIa was from Haematologic Technologies Inc., (Essex Jct., VT). FX was from Enzyme Research Laboratories Inc. (South Bend, IN), dioleoyl 1,2-diacyl-sn-glycero-3-(phospho-L-serine) (PS) and oleoyl 1,2-diacyl-sn-glycero-3-phosphocholine (PC) from Avanti Polar Lipids Inc. (Alabaster, AL). FIXa chromogenic substrate #299 was from American Diagnostica (Greenwich, CT). Actin FS and Innovin were obtained from Dade International Inc. (Miami, FL). SEPHAROSE™ resins and columns were from Amersham Pharmacia Biotech (Piscataway, NJ). DiaEthyleneglycol (analytical grade) and $FeCl_3$ (reagent grade) were from Mallinckrodt Inc. (Paris, KY). Fatty acid-free BSA was from Calbiochem (La Jolla, CA). Sodium heparin for injection was from Elkins Sinn Inc. (Cherry Hill, NJ). Sterile saline for injection was purchased from Baxter Healthcare Corp. (Deerfield, IL). Purified TF (1-243) from E.coli and recombinant F.VIIa were kindly provided by Robert F. Kelley (Genentech, Inc.).

Please replace the paragraph beginning on page 54, line 27 and endingpage 55 , line 24 with the following amended paragraph:

EXAMPLE 2

Methods

Biopanning procedure - A large library of 10^{10} scFv (Cambridge Antibody Technology, Cambridgeshire, UK) (Vaughan et al. (1996) Nature Biotechnology 14:309-314) was panned through two rounds of enrichment against biotinylated peptide. Affinity-driven selection (Hawkins et al., (1992) J. Mol. Biol. 226:889-896) was performed by decreasing the amount of antigen at each subsequent round of panning (100 nM and 10 nM, for rounds 1 and 2, respectively). To ensure proper conformation of the Gla peptide, calcium chloride (2 mM) was added to all solutions, unless indicated otherwise, during the panning procedure and all subsequent assays. For each selection, approximately 10^{12} titered units of phage, blocked in 1 ml of TBS containing 3% skimmed milk, 0.1% TWEEN® and 2 mM $CaCl_2$ (MTBST/Ca), were incubated for 1 hr at room temperature (RT) with the biotinylated peptide. Streptavidin-conjugated beads (DYNABEADS®, Dynal, Oslo Norway) blocked in MTBS, were added to the phage-biotinylated antigen mixture for 15 min. at RT. A volume of 300 µl of DYNABEADS® was used for round 1, and was decreased to 100 µl at round 2. The DYNABEADS® were washed three times with each of the following solutions-: TBST/Ca, MTBST/Ca, MTBS/Ca, and TBS/Ca, using a ~~Dynal MPC~~DYNAL MPC® (Magnetic Particle Concentrator). Bound phage were eluted step-wise with 4M $MgCl_2$, 1 mM Tetra-ethylamine (TEA), and 100 mM HCl. Each elution was performed at RT for 5 min, and eluted fractions were neutralized with 50 mM Tris-HCl, pH 7.5. Phage recovered after each round of panning were propagated in the bacterial suppressor strain TG1.

Please replace the paragraph on page 56, lines 11-31 with the following amended paragraph:

Methods

Clone characterization - MAXISORP™ Elisa plates (Nunc) were coated overnight at 4°C with Gla peptide (5 μg/ml) in HEPES buffered saline (HBS). Plates were blocked with HBS buffer containing 0.1% TWEEN® and 3% milk powder. Phage culture supernatants (50 μl) were directly applied to the plates. Horseradish peroxidase (HRP)-conjugated anti-M13 (Pharmacia, Uppsala, Sweden) was then added. DNA purified from selected clones was characterized by BstNI digestion and sequencing (ABI377, Perkin Elmer, Foster City, CA).

ScFv protein ELISA - ELISA plates were coated with either the anti-c myc antibody 9E10 in carbonate buffer (format I), FIX or FIX-related factors, in HBS with 2 mM $CaCl_2$ (HBSCa) (format II). Plates were blocked with HBSCa containing 0.1% TWEEN® (HBST/Ca). ScFv were added at a concentration of 5 μg/ml. In format I, biotinylated FIX (1μg) was applied to the plates followed by Streptavidin-HRP. In format II, detection of scFv was performed using 9E10 anti-c myc mAb and an HRP-conjugated goat anti-mouse Fc-specific mAb (Zymed, South San Francisco, CA). All reagent dilutions were prepared in blocking buffer HBST/Ca and plates were washed with HBS/Ca containing 0.05% ~~Tween~~TWEEN®.

Please replace the paragraph on page 60, lines 3-16 with the following amended paragraph:

For kinetics measurements, 2-fold serial dilutions (10 μL) of antibody were injected in running buffer (0.05% Tween-20, 150 mM NaCl, 2 mM $CaCl_2$, 10 mM Hepes pH 7.4) at 25°C using a flow rate of 10 uL/min. Regeneration was achieved with 4.5 M $MgCl_2$, followed by wash solution (50 mM EDTA, 150 mM NaCl, 0.05% TWEEN-20®). Equilibrium dissociation constants, Kd's, from SPR measurements were calculated as k_{off}/k_{on}. Dissociation data were fit to a simple 1:1 Langmuir binding model. Pseudo-first order rate constant (ks) were calculated for each association curve, and plotted as a function of protein concentration to obtain k_{on} +/- s.e. (standard error of fit). The resulting errors e[K] in calculated K_d's were calculated as follows:

$$e[K] = [(k_{on})^{-2}(s_{off})^2 + (k_{off})^2(k_{on})^{-4}(s_{on})^2]^{1/2}$$

where s_{off} and s_{on} are the standard errors in k_{on} and k_{off}, respectively.

Please replace the paragraph beginning on page 70, line 2 and ending on page 71, line 23 with the following rewritten paragraph:

Methods

Production and purification of –leucine-zippered 10C12 $F(ab')_2$ antibody. cDNAs encoding the variable heavy and light chain of clone 10C12 were amplified by PCR and subcloned into an expression vector containing both human heavy ($F_{d'}$) and light chain (lambda) constant regions (Carter et al. (1992) Bio/Technology 10:163-167) as well as a leucine zipper sequence (Kostelny et al. (1992), J. Immunol. 148:1547-1553) added at the 3' end of the constant heavy chain sequence. This vector was expressed in E. coli K12 strain 33B6 (fhuA phoA-delta-E15delta(argF-lac)169 deoC2 degP41(deltaPstI-kanR) IN(rrnDrrnE)1 ilvG2096), derived from the strain W3110. Cells were grown for 46 hours in an aerated 60 liter fermentor at 30^0C in a medium that initially contained 12 mg/l tetracycline, 12 g/l digested casein, 5 mM glucose, 47 mM $(NH4)_2SO_4$, 10 mM NaH_2PO_4, 18 mM K_2HPO_4, 4 mM trisodium citrate, 12 mM $MgSO_4$, 250 M $FeCl_3$, and 40 M each of $ZnSO_4$, $MnSO_2$, $CuSO_4$, $CoCl_2$, H_3BO_3, and $NaMoO_4$. The fermentation received an automated feed of ammonia:leucine (35:1 molar ratio) to maintain the pH at 7.0 and glucose, adjusted to the highest rate that would prevent acetate accumulation. Operating conditions were sufficient to supply oxygen at 3 mmol/l-min. Expression was induced by phosphate starvation. Final cell density was 160 OD_{550}. Harvested E. coli cell pellet was stored frozen at -70□C. The frozen pellet was broken into small pieces with a mallet and mixed with 5 volumes of 20 mM MES (2-{N-Morpholino}ethane-sulfonic acid)/2 M urea/5 mM EDTA/0.25 M NaCl, pH 5.0 (extraction buffer) using an ultraturax tissue homogenizer until a uniform suspension was achieved. The cell suspension was then passed through a homogenizer (Model 15M, Gaulin Corp., Everett, MA) to disrupt the cells. The extract was clarified by adjusting the mixture to pH 3.5 with 6 N HCl and centrifuging for 20 minutes at 6000 X g. The pH of the supernatant was readjusted to 5.0 using NaOH. The supernatant was conditioned for chromatography by dilution with 4 parts 20 mM MES/2 M urea, pH 5.0, filtered through a 0.2 micron filter (Millipore Corp., Bedford, MA) and applied to a SP-SEPHAROSE™ fast flow

cation exchange resin equilibrated in the dilution buffer. The column was washed extensively in the same buffer and then with 20 mM MES, pH 5.0. The column was eluted in two steps using 0.5 M NaCl and 1 M NaCl in 20 mM MES buffer, pH 5.0. The 10C12 leucine-zippered $F(ab')_2$ was recovered in the 1 M NaCl/20 mM MES fraction. The SP-SEPHAROSE™ pool was loaded in multiple cycles to a Protein G-SEPHAROSE™ fast flow column. The column was equilibrated and washed with 20 mM Tris/0.5 M NaCl, pH 7.5. Elution was with 0.1 M acetic acid/0.15 M NaCl, pH 3.0, and the column was regenerated after each cycle with 20 mM Tris/2 M guanidine HCl, pH 7.5. The combined protein G pools were concentrated approximately 20-fold using an Amicon stirred cell system (Amicon Inc., Beverly, MA) equipped with a YM30 membrane. The concentrated pool was buffer exchanged using a SEPHADEX™ G25 column run in 20 mM $NaPO_4$/0.15 M NaCl, pH 7.0. The G25 pool was passed through a Q-SEPHAROSE™ fast flow column in 20 mM $NaPO_4$/0.15M NaCl, pH 7.0, for endotoxin removal. The final pool contained 12.5 EU/mg protein and was passed through a 0.22 micron filter.

Please replace the paragraph beginning on page 71, line 31 and ending on page 72, line 19 with the following amended paragraph:

Arterial thrombosis model in the guinea pig. Experiments were performed as described by Carteaux et al. (1995), Circulation 91:1568-1574). GOHI male guinea pigs (350-450 g, BRL, Füllinsdorf, Switzerland) were anesthetized by i.–m. injection of– 40 mg/kg ketamine HCl (~~Ketasol~~KETASOL-100®, Gräub AG, Bern, Switzerland) and 5 mg/kg xylazine 2% (~~Rompun~~ROMPUN®, Bayer AG, Leverkusen, Germany). A catheter pressure transducer (Millar 2F Mikro-Tip SPC-320 Millar Instr. Inc. Houston, TX) was inserted into the right femoral artery to measure blood pressure and heart rate. Into the left femoral artery was placed a catheter (~~TriCath In 22G~~TRICATH IN 22G™, Codan, Espergaerde,DK) for blood sampling. A left jugular vein catheter (~~TriCath In 22G~~TRICATH IN 22G™) was also inserted for drug administration. The right carotid artery was dissected free and a 0.8 mm diameter silicone cuff-type Doppler flow probe (type D-20-0.8, Iowa Doppler Products, IA) was connected to a 20

MHz pulsed Doppler flowmeter module (System 6-Model 202, Triton Technology, Inc. San Diego, CA) to monitor the blood flow velocity. Blood pressure (mm Hg), heart rate (beats/min) and carotid blood flow velocity (Volts) were recorded on a Graphtec Linear recorder VII (Model WR 3101, Hugo Sachs, March-Hugstetten, Germany).